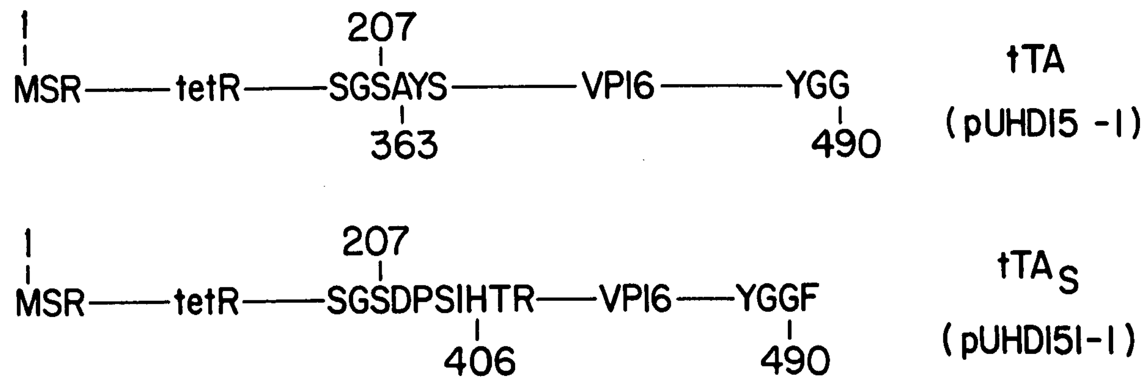

1
MSR
tetR
207
SGSAYS
363
VP16
YGG
490
tTA
(pUHD15 -1)
1
MSR
tetR
207
SGSDPSIHTR
406
VP16
YGGF
490
tTA_S
(pUHD151-1)

FIG. 1A

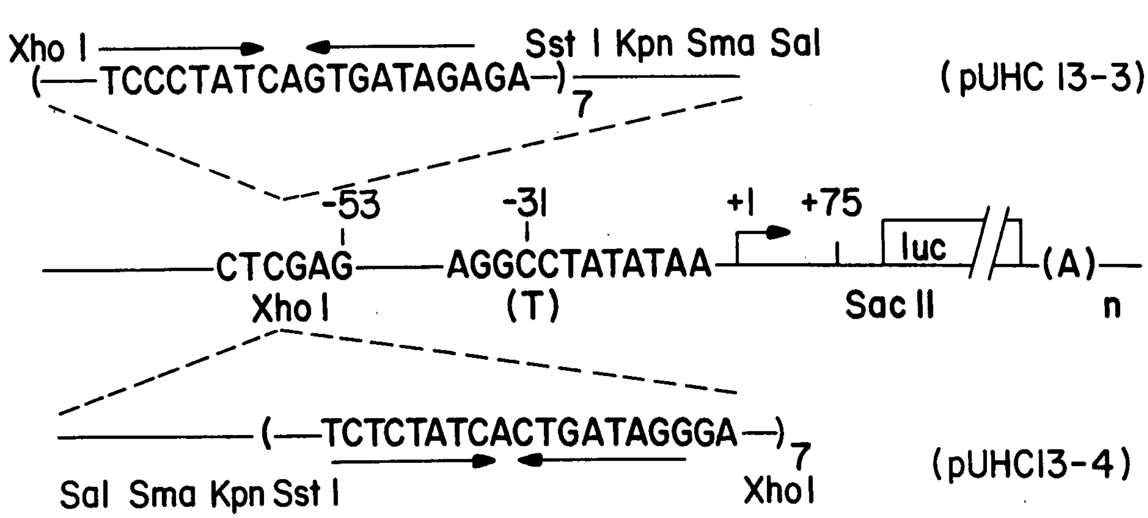

Xho I
Sst I Kpn Sma Sal
$(\text{—TCCCTATCAGTGATAGAGA—})_7$
(pUHC 13-3)
-53
-31
+1
+75
CTCGAG
AGGCCTATATAA
(T)
Xho I
luc
Sac II
$(A)_n$
$(\text{—TCTCTATCACTGATAGGGA—})_7$
Sal Sma Kpn Sst I
Xho I
(pUHC13-4)

FIG. 1B

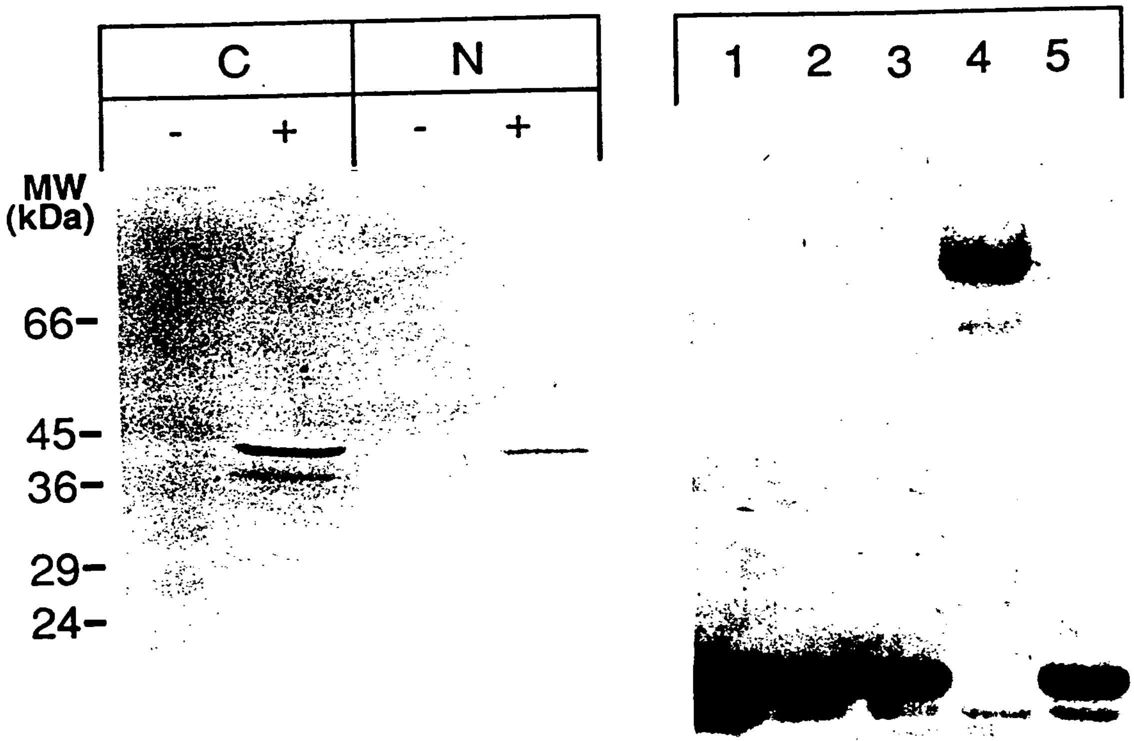


FIG. 2A FIG. 2B

FIG. 3A

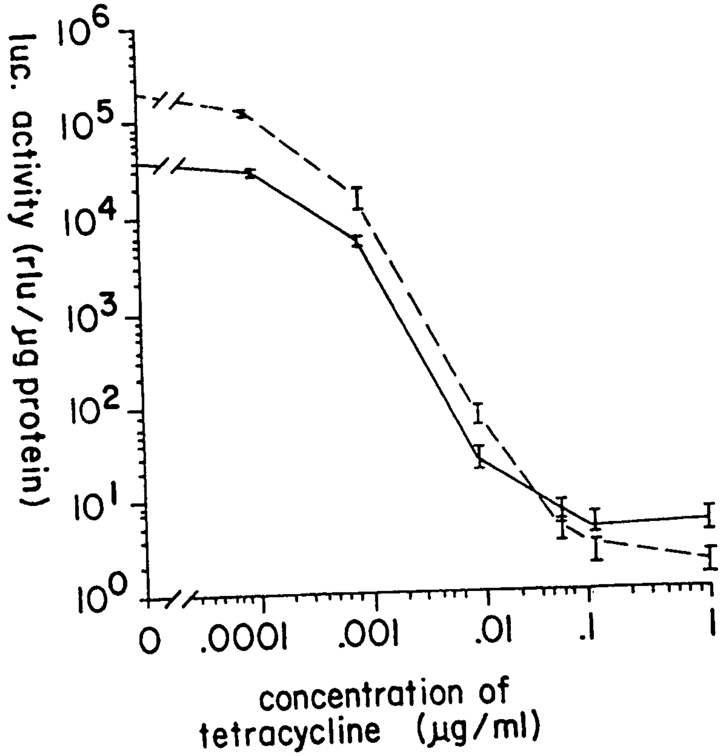
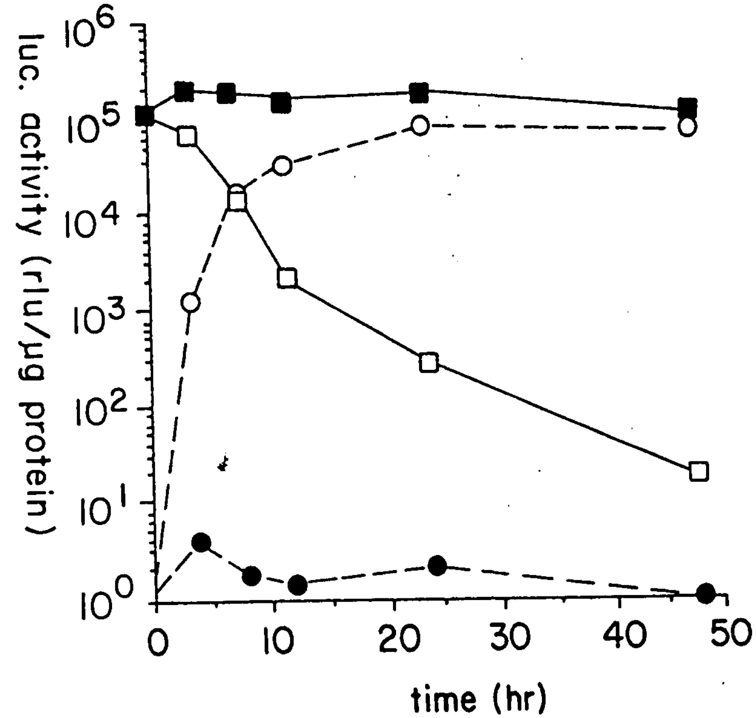

luc. activity (rlu/μg protein)
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0
.0001
.001
.01
.1
1
concentration of
tetracycline (μg/ml)

FIG. 3B


luc. activity (rlu/μg protein)
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0
10
20
30
40
50
time (hr)

ATG TCT AGA TTA GAT AAA AGT AAA GTG ATT AAC AGC GCA TTA GAG CTG CTT AAT
Met Ser Arg Leu Asp Lys Ser Lys Val Ile Asn Ser Ala Leu Glu Leu Leu Asn

GAG GTC GGA ATC GAA GGT TTA ACA ACC CGT AAA CTC GCC CAG AAG CTA GGT GTA
Glu Val Gly Ile Glu Gly Leu Thr Thr Arg Lys Leu Ala Gln Lys Leu Gly Val

GAG CAG CCT ACA TTG TAT TGG CAT GTA AAA AAT AAG CGG GCT TTG CTC GAC GCC
Glu Gln Pro Thr Leu Tyr Trp His Val Lys Asn Lys Arg Ala Leu Leu Asp Ala

TTA GCC ATT GAG ATG TTA GAT AGG CAC CAT ACT CAC TTT TGC CCT TTA GAA GGG
Leu Ala Ile Glu Met Leu Asp Arg His His Thr His Phe Cys Pro Leu Glu Gly

GAA AGC TGG CAA GAT TTT TTA CGT AAT AAG GCT AAA AGT TTT AGA TGT GCT TTA
Glu Ser Trp Gln Asp Phe Leu Arg Asn Lys Ala Lys Ser Phe Arg Cys Ala Leu

Fig. 4A

CTA AGT CAT CGC GAT GGA GCA AAA GTA CAT TTA GGT ACA CGG CCT ACA GAA AAA
Leu Ser His Arg Asp Gly Ala Lys Val His Leu Gly Thr Arg Pro Thr Glu Lys

CAG TAT GAA ACT CTC GAA AAT CAA TTA GCC TTT TTA TGC CAA CAA GGT TTT TCA
Gln Tyr Glu Thr Leu Glu Asn Gln Leu Ala Phe Leu Cys Gln Gln Gly Phe Ser

CTA GAG AAT GCA TTA TAT GCA CTC AGC GCT GTG GGG CAT TTT ACT TTA GGT TGC
Leu Glu Asn Ala Leu Tyr Ala Leu Ser Ala Val Gly His Phe Thr Leu Gly Cys

GTA TTG GAA GAT CAA GAG CAT CAA GTC GCT AAA GAA GAA AGG GAA ACA CCT ACT
Val Leu Glu Asp Gln Glu His Gln Val Ala Lys Glu Glu Arg Glu Thr Pro Thr

ACT GAT AGT ATG CCG CCA TTA TTA CGA CAA GCT ATC GAA TTA TTT GAT CAC CAA
Thr Asp Ser Met Pro Pro Leu Leu Arg Gln Ala Ile Glu Leu Phe Asp His Gln

Fig. 4B

```
GGT GCA GAG CCA GCC TTC TTA TTC GGC CTT GAA TTG ATC ATA TGC GGA TTA GAA
Gly Ala Glu Pro Ala Phe Leu Phe Gly Leu Glu Leu Ile Ile Cys Gly Leu Glu

AAA CAA CTT AAA TGT GAA AGT GGG TCC GCG TAC AGC CGC GCG CGT ACG AAA AAC
Lys Gln Leu Lys Cys Glu Ser Gly Ser Ala Tyr Ser Arg Ala Arg Thr Lys Asn

AAT TAC GGG TCT ACC ATC GAG GGC CTG CTC GAT CTC CCG GAC GAC GAC GCC CCC
Asn Tyr Gly Ser Thr Ile Glu Gly Leu Leu Asp Leu Pro Asp Asp Asp Ala Pro

GAA GAG GCG GGG CTG GCG GCT CCG CGC CTG TCC TTT CTC CCC GCG GGA CAC ACG
Glu Glu Ala Gly Leu Ala Ala Pro Arg Leu Ser Phe Leu Pro Ala Gly His Thr

CGC AGA CTG TCG ACG GCC CCC CCG ACC GAT GTC AGC CTG GGG GAC GAG CTC CAC
Arg Arg Leu Ser Thr Ala Pro Pro Thr Asp Val Ser Leu Gly Asp Glu Leu His
```

Fig. 4C

```
TTA GAC GGC GAG GAC GTG GCG ATG GCG CAT GCC GAC GCG CTA GAC GAT TTC GAT
Leu Asp Gly Glu Asp Val Ala Met Ala His Ala Asp Ala Leu Asp Asp Phe Asp

CTG GAC ATG TTG GGG GAC GGG GAT TCC CCG GGT CCG GGA TTT ACC CCC CAC GAC
Leu Asp Met Leu Gly Asp Gly Asp Ser Pro Gly Pro Gly Phe Thr Pro His Asp

TCC GCC CCC TAC GGC GCT CTG GAT ATG GCC GAC TTC GAG TTT GAG CAG ATG TTT
Ser Ala Pro Tyr Gly Ala Leu Asp Met Ala Asp Phe Glu Phe Glu Gln Met Phe

ACC GAT CCC CTT GGA ATT GAC GAG TAC GGT GGG TAG
Thr Asp Pro Leu Gly Ile Asp Glu Tyr Gly Gly  *
```

Fig. 4D

ATG TCT AGA TTA GAT AAA AGT AAA GTG ATT AAC AGC GCA TTA GAG CTG CTT AAT
Met Ser Arg Leu Asp Lys Ser Lys Val Ile Asn Ser Ala Leu Glu Leu Leu Asn

GAG GTC GGA ATC GAA GGT TTA ACA ACC CGT AAA CTC GCC CAG AAG CTA GGT GTA
Glu Val Gly Ile Glu Gly Leu Thr Thr Arg Lys Leu Ala Gln Lys Leu Gly Val

GAG CAG CCT ACA TTG TAT TGG CAT GTA AAA AAT AAG CGG GCT TTG CTC GAC GCC
Glu Gln Pro Thr Leu Tyr Trp His Val Lys Asn Lys Arg Ala Leu Leu Asp Ala

TTA GCC ATT GAG ATG TTA GAT AGG CAC CAT ACT CAC TTT TGC CCT TTA GAA GGG
Leu Ala Ile Glu Met Leu Asp Arg His His Thr His Phe Cys Pro Leu Glu Gly

GAA AGC TGG CAA GAT TTT TTA CGT AAT AAC GCT AAA AGT TTT AGA TGT GCT TTA
Glu Ser Trp Gln Asp Phe Leu Arg Asn Asn Ala Lys Ser Phe Arg Cys Ala Leu

Fig. 5A

CTA AGT CAT CGC GAT GGA GCA AAA GTA CAT TTA GGT ACA CGG CCT ACA GAA AAA
Leu Ser His Arg Asp Gly Ala Lys Val His Leu Gly Thr Arg Pro Thr Glu Lys

CAG TAT GAA ACT CTC GAA AAT CAA TTA GCC TTT TTA TGC CAA CAA GGT TTT TCA
Gln Tyr Glu Thr Leu Glu Asn Gln Leu Ala Phe Leu Cys Gln Gln Gly Phe Ser

CTA GAG AAT GCA TTA TAT GCA CTC AGC GCT GTG GGG CAT TTT ACT TTA GGT TGC
Leu Glu Asn Ala Leu Tyr Ala Leu Ser Ala Val Gly His Phe Thr Leu Gly Cys

GTA TTG GAA GAT CAA GAG CAT CAA GTC GCT AAA GAA GAA AGG GAA ACA CCT ACT
Val Leu Glu Asp Gln Glu His Gln Val Ala Lys Glu Glu Arg Glu Thr Pro Thr

ACT GAT AGT ATG CCG CCA TTA TTA CGA CAA GCT ATC GAA TTA TTT GAT CAC CAA
Thr Asp Ser Met Pro Pro Leu Leu Arg Gln Ala Ile Glu Leu Phe Asp His Gln

Fig. 5B

GGT GCA GAG CCA GCC TTC TTA TTC GGC CTT GAA TTG ATC ATA TGC GGA TTA GAA
Gly Ala Glu Pro Ala Phe Leu Phe Gly Leu Glu Leu Ile Ile Cys Gly Leu Glu

AAA CAA CTT AAA TGT GAA AGT GGG TCT GAT CCA TCG ATA CAC ACG CGC AGA CTG
Lys Gln Leu Lys Cys Glu Ser Gly Ser Asp Pro Ser Ile His Thr Arg Arg Leu

TCG ACG GCC CCC CCG ACC GAT GTC AGC CTG GGG GAC GAG CTC CAC TTA GAC GGC
Ser Thr Ala Pro Pro Thr Asp Val Ser Leu Gly Asp Glu Leu His Leu Asp Gly

GAG GAC GTG GCG ATG GCG CAT GCC GAC GCG CTA GAC GAT TTC GAT CTG GAC ATG
Glu Asp Val Ala Met Ala His Ala Asp Ala Leu Asp Asp Phe Asp Leu Asp Met

TTG GGG GAC GGG GAT TCC CCG GGT CCG GGA TTT ACC CCC CAC GAC TCC GCC CCC
Leu Gly Asp Gly Asp Ser Pro Gly Pro Gly Phe Thr Pro His Asp Ser Ala Pro

Fig. 5C

TAC GGC GCT CTG GAT ATG GCC GAC TTC GAG TTT GAG CAG ATG TTT ACC GAT GCC
Tyr Gly Ala Leu Asp Met Ala Asp Phe Glu Phe Glu Gln Met Phe Thr Asp Ala

CTT GGA ATT GAC GAG TAC GGT GGG TTC TAG
Leu Gly Ile Asp Glu Tyr Gly Gly Phe *

Fig 5D

GAATTCCTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTC

CCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGT

GAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCC

TATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGA

AAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGCTCGGTACCCGGGT

CGAGTAGGCGTGTACGGTGGGAGGCC<u>TATATAA</u>GCAGAGCTCGTTTAGTGAACCGTCAGATCGC

CTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGC

GG

Fig. 6

GAATTCCTCGACCCGGGTACCGAGCTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTA

AACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCT

ATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAA

CTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTAT

CACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACT

CGAGTAGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGC

CTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGC

GG

Fig. 7

GAGCTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTC

TATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAA

ACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTA

TCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAAC

TCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGAGATCCGGCGAATTCGAAC

ACGCAGATGCAGTCGGGGCGGCGCGGTCCGAGGTCCACTTCGCATATTAAGGTGACGCGTGTGG

CCTCGAACACCGAG

Fig. 8

CTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATC

AGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGT

CGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAG

TGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCG

AGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGCTCGGTACCCGGGTCGAGTA

GGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAG

ACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCCC

GAATTCGAGCTCGGTACCGGGCCCCCCCTCGAGGTCGACGGTATCGATAAGCTTGATATCGAAT

TCCAGGAGGTGGAGATCCGCGGGTCCAGCCAAACCCCACACCCATTTTCTCCTCCCTCTGCCCC

TATATCCCGGCACCCCCTCCTCCTAGCCCTTTCCCTCCTCCCGAGAGACGGGGGAGGAGAAAAG

GGGAGTTCAGGTCGACATGACTGAGCTGAAGGCAAAGGAACCTCGGGCTCCCCACGTGGCGGGC

GGCGCGCCCTCCCCCACCGAGGTCGGATCCCAGCTCCTGGGTCGCCCGGACCCTGGCCCCTTCC

AGGGGAGCCAGACCTCAGAGGCCTCGTCTGTAGTCTCCGCCATCCCCATCTCCCTGGACGGGTT

Fig. 9A

GCTCTTCCCCCGGCCCTGTCAGGGGCAGAACCCCCCAGACGGGAAGACGCAGGACCCACCGTCG

TTGTCAGACGTGGAGGGCGCATTTCCTGGAGTCGAAGCCCCGGAGGGGGCAGGAGACAGCAGCT

CGAGACCTCCAGAAAAGGACAGCGGCCTGCTGGACAGTGTCCTCGACACGCTCCTGGCGCCCTC

GGGTCCCGGGCAGAGCCACGCCAGCCCTGCCACCTGCGAGGCCATCAGCCCGTGGTGCCTGTTT

GGCCCCGACCTTCCCGAAGACCCCCGGGCTGCCCCCGCTACCAAAGGGGTGTTGGCCCCGCTCA

TGAGCCGACCCGAGGACAAGGCAGGCGACAGCTCTGGGACGGCAGCGGCCCACAAGGTGCTGCC

CAGGGGACTGTCACCATCCAGGCAGCTGCTGCTCCCCTCCTCTGGGAGCCCTCACTGGCCGGCA

GTGAAGCCATCCCCGCAGCCCGCTGCGGTGCAGGTAGACGAGGAGGACAGCTCCGAATCCGAGG

GCACCGTGGGCCCGCTCCTGAAGGGCCAACCTCGGGCACTGGGAGGCACGGCGGCCGGAGGAGG

AGCTGCCCCCGTCGCGTCTGGAGCGGCCGCAGGAGGCGTCGCCCTTGTCCCCAAGGAAGATTCT

CGCTTCTCGGCGCCCAGGGTCTCCTTGGCGGAGCAGGACGCGCCGGTGGCGCCTGGCGCTCCC

CGCTGGCCACCTCGGTGGTGGATTTCATCCACGTGCCCATCCTGCCTCTCAACCACGCTTTCCT

GGCCACCCGCACCAGGCAGCTGCTGGAGGGGGAGAGCTACGACGGCGGGGCCGCGGCCGCCAGC

Fig. 9B

CCCTTCGTCCCGCAGCGGGGCTCCCCCTCTGCCTCGTCCACCCCTGTGGCGGGCGGCGACTTCC
CCGACTGCACCTACCCGCCCGACGCCGAGCCCAAAGATGACGCGTTCCCCCTCTACGGCGACTT
CCAGCCGCCCGCCCTCAAGATAAAGGAGGAGGAAGAAGCCGCCGAGGCCGCGGCGCGCTCCCCG
CGTACGTACCTGGTGGCTGGTGCAAACCCCGCCGCCTTCCCGGACTTCCAGCTGGCAGCGCCGC
CGCCACCCTCGCTGCCGCCTCGAGTGCCCTCGTCCAGACCCGGGGAAGCGGCGGTGGCGGCCTC
CCCAGGCAGTGCCTCCGTCTCCTCCTCGTCCTCGTCGGGGTCGACCCTGGAGTGCATCCTGTAC
AAGGCAGAAGGCGCGCCGCCCCAGCAGGGCCCCTTCGCGCCGCTGCCCTGCAAGCCTCCGGGCG
CCGGCGCCTGCCTGCTCCCGCGGGACGGCCTGCCCTCCACCTCCGCCTCGGGCGCAGCCGCCGG
GGCCGCCCCTGCGCTCTACCCGACGCTCGGCCTCAACGGACTCCCGCAACTCGGCTACCAGGCC
GCCGTGCTCAAGGAGGGCCTGCCGCAGGTCTACACGCCCTATCTCAACTACCTGAGGCCGGATT
CAGAAGCCAGTCAGAGCCCACAGTACAGCTTCGAGTCACTACCTCAGAAGATTTGTTTGATCTG
TGGGGATGAAGCATCAGGCTGTCATTATGGTGTCCTCACCTGTGGGAGCTGTAAGGTCTTCTTT
AAAAGGGCAATGGAAGGGCAGCATAACTATTTATGTGCTGGAAGAAATGACTGCATTGTTGATA

Fig. 9C

AAATCCGCAGGAAAAACTGCCCGGCGTGTCGCCTTAGAAAGTGCTGTCAAGCTGGCATGGTCCT

TGGAGGGCGAAAGTTTAAAAAGTTCAATAAAGTCAGAGTCATGAGAGCACTCGATGCTGTTGCT

CTCCCACAGCCAGTGGGCATTCCAAATGAAAGCCAACGAATCACTTTTTCTCCAAGTCAAGAGA

TACAGTTAATTCCCCCTCTAATCAACCTGTTAATGAGCATTGAACCAGATGTGATCTATGCAGG

ACATGACAACACAAAGCCTGATACCTCCAGTTCTTTGCTGACGAGTCTTAATCAACTAGGCGAG

CGGCAACTTCTTTCAGTGGTAAAATGGTCCAAATCTCTTCCAGGTTTTCGAAACTTACATATTG

ATGACCAGATAACTCTCATCCAGTATTCTTGGATGAGTTTAATGGTATTTGGACTAGGATGGAG

ATCCTACAAACATGTCAGTGGGCAGATGCTGTATTTTGCACCTGATCTAATATTAAATGAACAG

CGGATGAAAGAATCATCATTCTATTCACTATGCCTTACCATGTGGCAGATACCGCAGGAGTTTG

TCAAGCTTCAAGTTAGCCAAGAAGAGTTCCTCTGCATGAAAGTATTACTACTTCTTAATACAAT

TCCTTTGGAAGGACTAAGAAGTCAAAGCCAGTTTGAAGAGATGAGATCAAGCTACATTAGAGAG

CTCATCAAGGCAATTGGTTTGAGGCAAAAAGGAGTTGTTTCCAGCTCACAGCGTTTCTATCAGC

TCACAAAACTTCTTGATAACTTGCATGATCTTGTCAAACAACTTCACCTGTACTGCCTGAATAC

Fig. 9D

ATTTATCCAGTCCCGGGCGCTGAGTGTTGAATTTCCAGAAATGATGTCTGAAGTTATTGCTGCA

CAGTTACCCAAGATATTGGCAGGGATGGTGAAACCACTTCTCTTTCATAAAAAGTGAATGTCAA

TTATTTTTCAAAGAATTAAGTGTTGTGGTATGTCTTTCGTTTTGGTCAGGATTATGACGTCTCG

AGTTTTTATAATATTCTGAAAGGGAATTCCTGCAGCCCGGGGGATCCACTAGTTCTAGAGGATC

CAGACATGATAAGATACATTGATGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATG

CTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAA

GTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTT

AAAGCAAGTAAAACCTCTACAAATGTGGTATGGCTGATTATGATCCTGCAAGCCTCGTCGTCTG

GCCGGACCACGCTATCTGTGCAAGGTCCCCGGACGCGCTCCATGAGCAGAGCGCCCGCCGCC

GAGGCAAGACTCGGGCGGCGCCCTGCCCGTCCCACCAGGTCAACAGGCGGTAACCGGCCTCTTC

ATCGGGAATGCGCGCGACCTTCAGCATCGCCGGCATGTCCCCTGGCGGACGGGAAGTATCAGCT

CGACCAAGCTTGGCGAGATTTTCAGGAGCTAAGGAAGCTAAAATGGAGAAAAAAATCACTGGAT

ATACCACCGTTGATATATCCCAATGGCATCGTAAAGAACATTTTGAGGCATTTCAGTCAGTTGC

Fig. 9E

TCAATGTACCTATAACCAGACCGTTCAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGC

GGTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGC

TGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAA

CGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTG

CTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGA

GGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCG

CTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG

GCGCTTTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG

GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGA

GTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGA

GCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAA

GGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTC

TTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACG

Fig. 9F

CGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGA

ACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCT

TTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGT

TACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTG

CCTGACTCCCCGTCGTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGC

AATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGA

AGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC

GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGG

CATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGG

CGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTG

TCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTAC

TGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAA

TAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATA

Fig. 9G

GCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTT

ACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTT

ACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAA

GGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCA

GGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTT

CCGCGCACATTTCCCCGAAAAGTGCCACCTGACGTCTAAGAAACCATTATTATCATGACATTAA

CCTATAAAAATAGGCGTATCACGAGGCCCTTTCGTC

Fig. 9H

CTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATC

AGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGT

CGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAG

TGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCG

AGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGCTCGGTACCCGGGTCGAGTA

GGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAG

ACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCCC

GAATTCCGCCCACGACCATGACCATGACCCTCCACACCAAAGCATCTGGGATGGCCCTACTGCA

TCAGATCCAAGGGAACGAGCTGGAGCCCCTGAACCGTCCGCAGCTCAAGATCCCCCTGGAGCGG

CCCCTGGGCGAGGTGTACCTGGACAGCAGCAAGCCCGCCGTGTACAACTACCCCGAGGGCGCCG

CCTACGAGTTCAACGCCGCGGCCGCCGCCAACGCGCAGGTCTACGGTCAGACCGGCCTCCCCTA

CGGCCCCGGGTCTGAGGCTGCGGCGTTCGGCTCCAACGGCCTGGGGGTTTCCCCCCACTCAAC

AGCGTGTCTCCGAGCCCGCTGATGCTACTGCACCCGCCGCCGCAGCTGTCGCCTTTCCTGCAGC

Fig. 10A

CCCACGGCCAGCAGGTGCCCTACTACCTGGAGAACGAGCCCAGCGGCTACACGGTGCGCGAGGC

CGGCCCGCCGGCATTCTACAGGCCAAATTCAGATAATCGACGCCAGGGTGGCAGAGAAAGATTG

GCCAGTACCAATGACAAGGGAAGTATGGCTATGGAATCTGCCAAGGAGACTCGCTACTGTGCAG

TGTGCAATGACTATGCTTCAGGCTACCATTATGGAGTCTGGTCCTGTGAGGGCTGCAAGGCCTT

CTTCAAGAGAAGTATTCAAGGACATAACGACTATATGTGTCCAGCCACCAACCAGTGCACCATT

GATAAAAACAGGAGGAAGAGCTGCCAGGCCTGCCGGCTCCGCAAATGCTACGAAGTGGGAATGA

TGAAAGGTGGGATACGAAAAGACCGAAGAGGAGGGAGAATGTTGAAACACAAGCGCCAGAGAGA

TGATGGGGAGGGCAGGGGTGAAGTGGGGTCTGCTGGAGACATGAGAGCTGCCAACCTTTGGCCA

AGCCCGCTCATGATCAAACGCTCTAAGAAGAACAGCCTGGCCTTGTCCCTGACGGCCGACCAGA

TGGTCATGGCCTTGTTGGATGCTGAGCCCCCCATACTCTATTCCGAGTATGATCCTACCAGACC

CTTCAGTGAAGCTTCGATGATGGGCTTACTGACCAACCTGGCAGACAGGGAGCTGGTTCACATG

ATCAACTGGGCGAAGAGGGTGCCAGGCTTTGTGGATTTGACCCTCCATGATCAGGTCCACCTTC

TAGAATGTGCCTGGCTAGAGATCCTGATGATTGGTCTCGTCTGGCGCTCCATGGAGCACCCAGT

Fig. 10B

GAAGCTACTGTTTGCTCCTAACTTGCTCTTGGACAGGAACCAGGGAAAATGTGTAGAGGGCATG
GTGGAGATCTTCGACATGCTGCTGGCTACATCATCTCGGTTCCGCATGATGAATCTGCAGGGAG
AGGAGTTTGTGTGCCTCAAATCTATTATTTTGCTTAATTCTGGAGTGTACACATTTCTGTCCAG
CACCCTGAAGTCTCTGGAAGAGAAGGACCATATCCACCGAGTCCTGGACAAGATCACAGACACT
TTGATCCACCTGATGGCCAAGGCAGGCCTGACCCTGCAGCAGCAGCACCAGCGGCTGGCCCAGC
TCCTCCTCATCCTCTCCCACATCAGGCACATGAGTAACAAAGGCATGGAGCATCTGTACAGCAT
GAAGTGCAAGAACGTGGTGCCCCTCTATGACCTGCTGCTGGAGATGCTGGACGCCCACCGCCTA
CATGCGCCCACTAGCCGTGGAGGGGCATCCGTGGAGGAGACGGACCAAAGCCACTTGGCCACTG
CGGGCTCTACTTCATCGCATTCCTTGCAAAAGTATTACATCACGGGGGAGGCAGAGGGTTTCCC
TGCCACAGTCTGAGAGCTCCCTGGCGGAATTCGAGCTCGGTACCCGGGGATCCTCTAGAGGATC
CAGACATGATAAGATACATTGATGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATG
CTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAA
GTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTT

Fig. 10C

AAAGCAAGTAAAACCTCTACAAATGTGGTATGGCTGATTATGATCCTGCAAGCCTCGTCGTCTG

GCCGGACCACGCTATCTGTGCAAGGTCCCCGGACGCGCGCTCCATGAGCAGAGCGCCCGCCGCC

GAGGCAAGACTCGGGCGGCGCCCTGCCCGTCCCACCAGGTCAACAGGCGGTAACCGGCCTCTTC

ATCGGGAATGCGCGCGACCTTCAGCATCGCCGGCATGTCCCCTGGCGGACGGGAAGTATCAGCT

CGACCAAGCTTGGCGAGATTTTCAGGAGCTAAGGAAGCTAAAATGGAGAAAAAAATCACTGGAT

ATACCACCGTTGATATATCCCAATGGCATCGTAAAGAACATTTTGAGGCATTTCAGTCAGTTGC

TCAATGTACCTATAACCAGACCGTTCAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGC

GGTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGC

TGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAA

CGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTG

CTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGA

GGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCG

CTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG

Fig. 10D

GCGCTTTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG

GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGA

GTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGA

GCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAA

GGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTC

TTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACG

CGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGA

ACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCT

TTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGT

TACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTG

CCTGATCCCCGTCGTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCA

ATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAA

GGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCG

Fig. 10E

GGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGC

ATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGC

GAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGT

CAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACT

GTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAAT

AGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATAG

CAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTA

CCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTA

CTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAG

GGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAG

GGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTC

CGCGCACATTTCCCCGAAAAGTGCCACCTGACGTCTAAGAAACCATTATTATCATGACATTAAC

CTATAAAAATAGGCGTATCACGAGGCCCTTTCGTC

Fig. 10F

FIG. 11

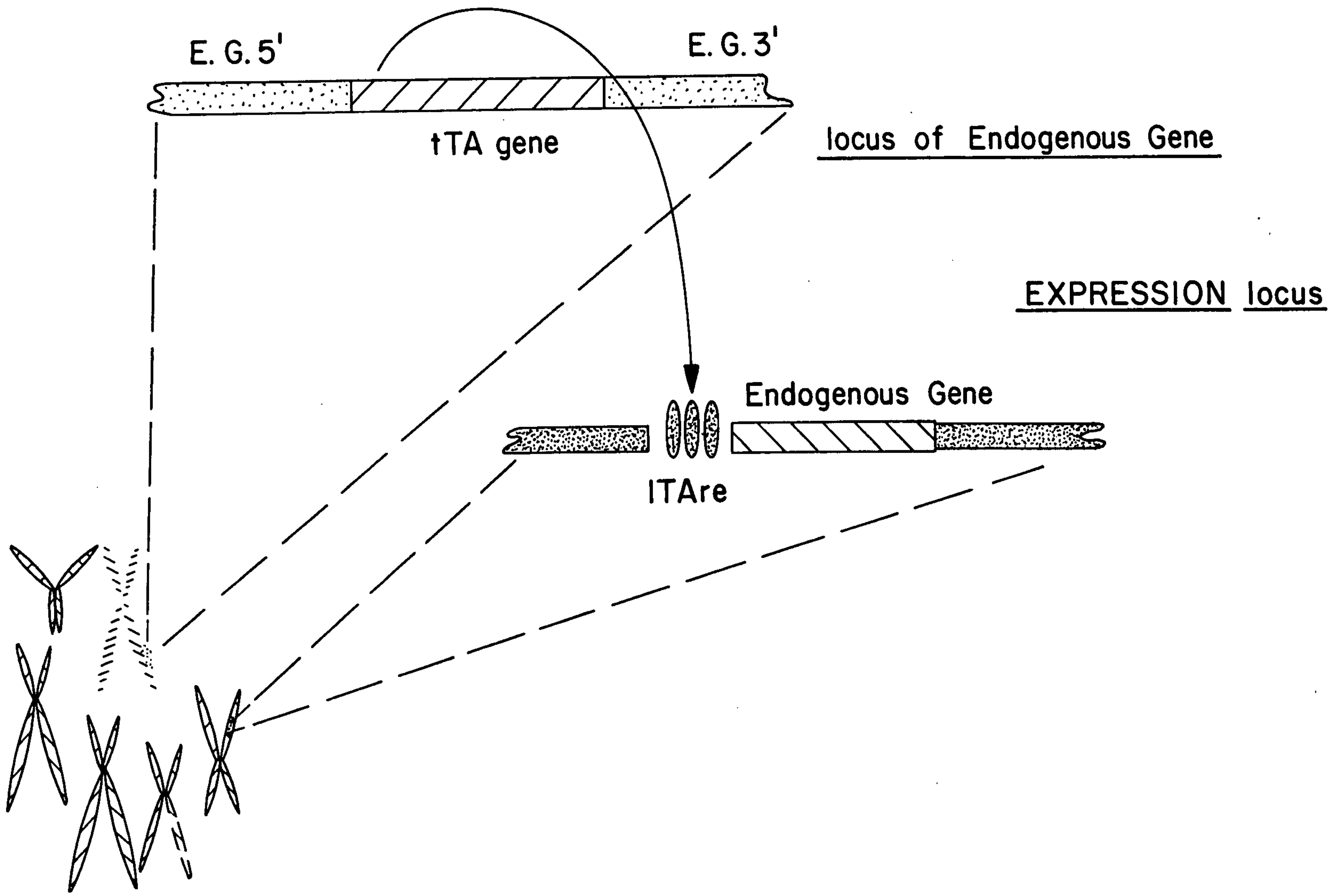
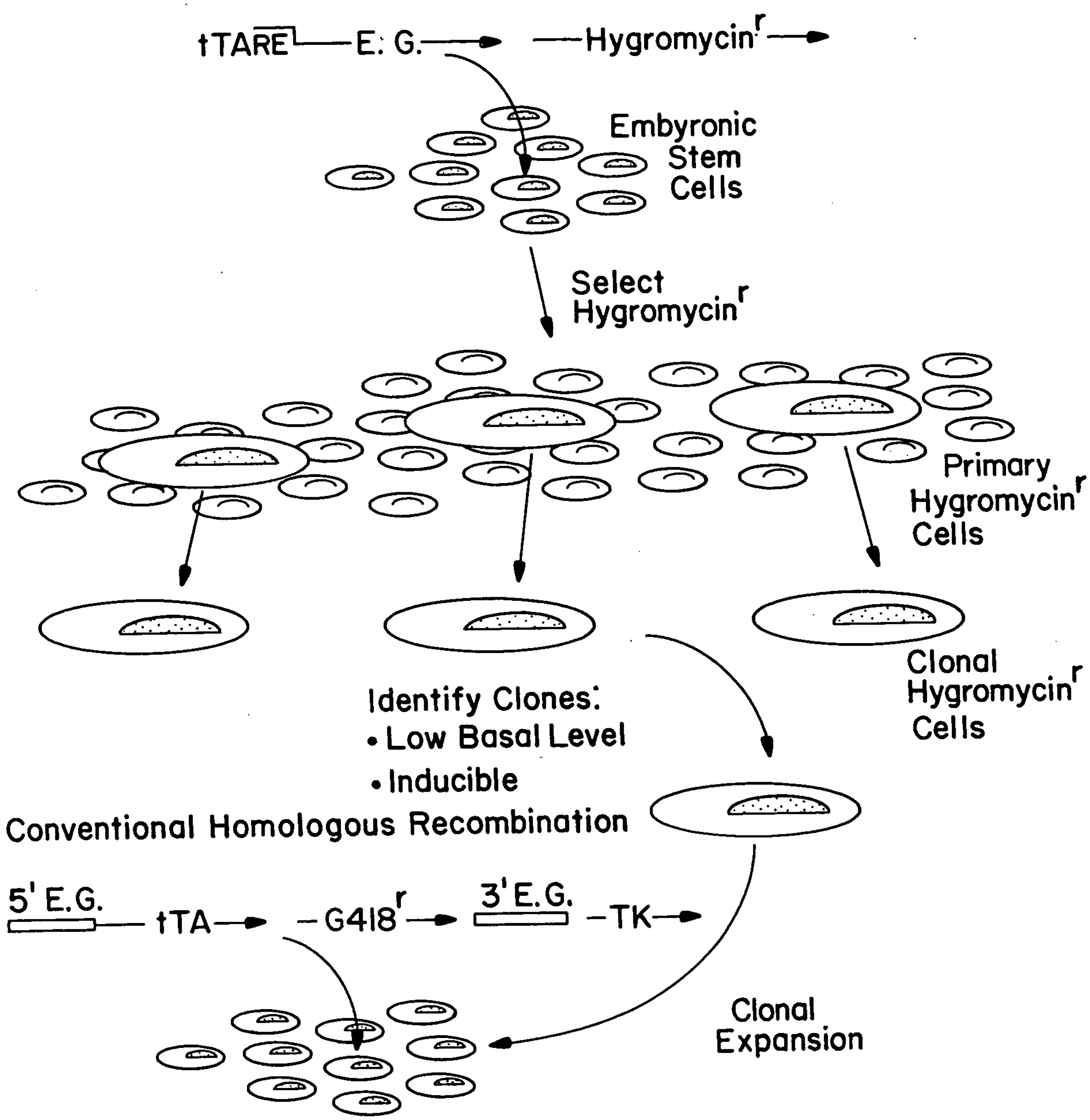

E. G. 5'
E. G. 3'
tTA gene
locus of Endogenous Gene
EXPRESSION locus
Endogenous Gene
ITAre

FIG. 12



tTARE — E. G. — Hygromycin^r
Embyronic Stem Cells
Select Hygromycin^r
Primary Hygromycin^r Cells
Clonal Hygromycin^r Cells
Identify Clones:
• Low Basal Level
• Inducible
Conventional Homologous Recombination
5' E.G. — tTA — G418^r — 3' E.G. — TK
Clonal Expansion

FIG. 13A

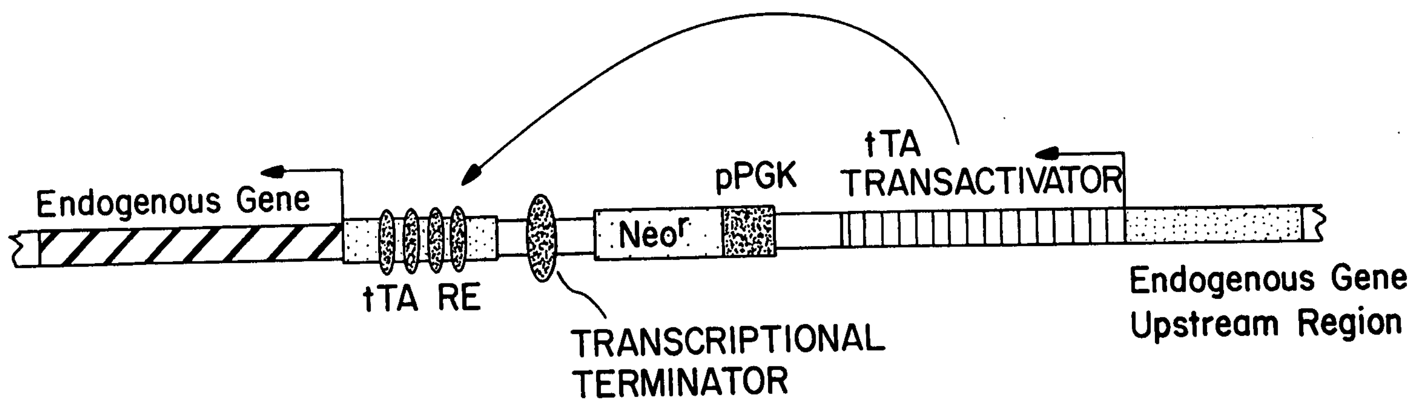


FIG. 13B

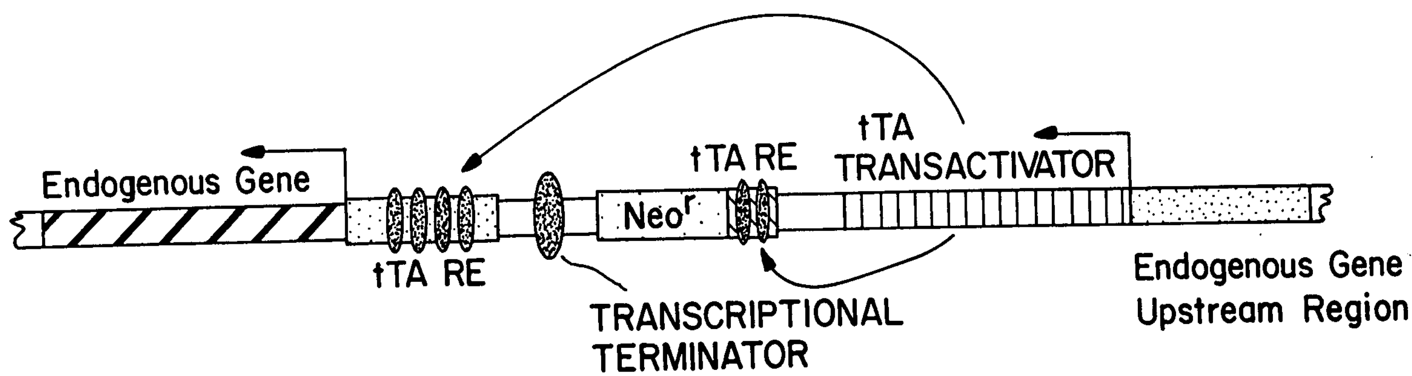
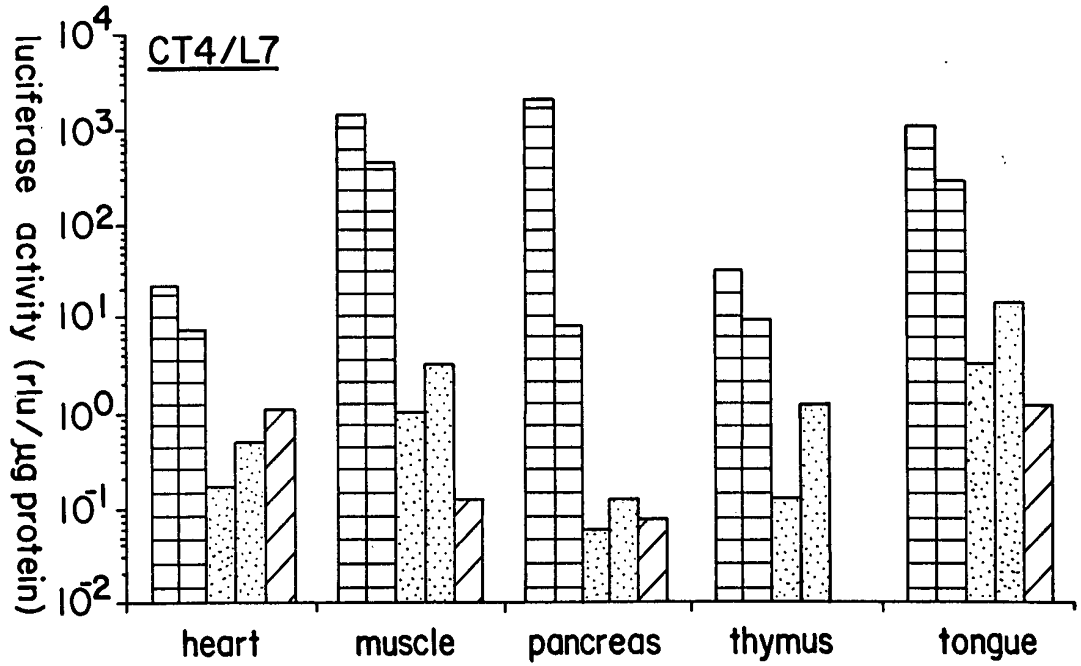


FIG.14


CT4/L7
luciferase activity (rlu/µg protein)
10^4
10^3
10^2
10^1
10^0
10^{-1}
10^{-2}
heart
muscle
pancreas
thymus
tongue

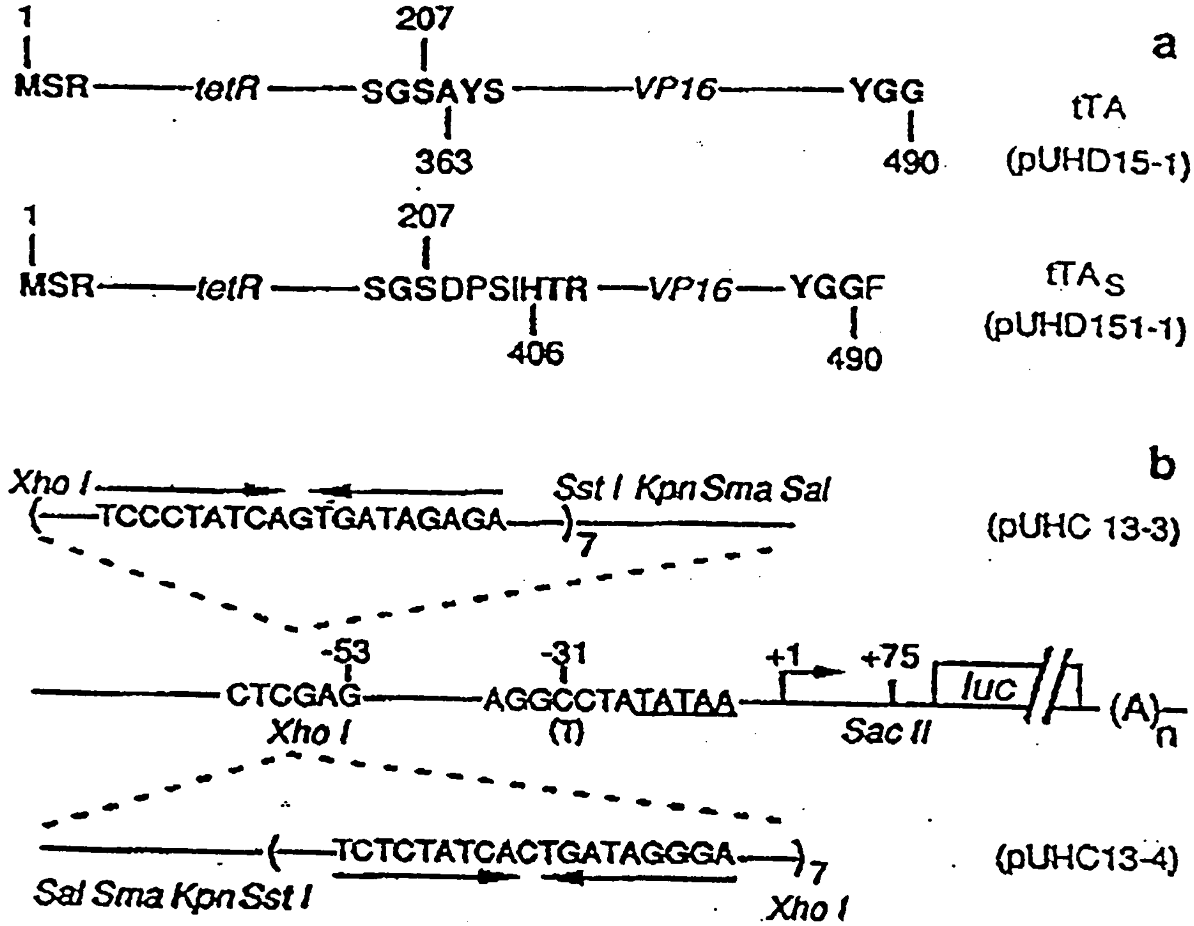

1
207
a
MSR
tetR
SGSAYS
VP16
YGG
tTA
363
490
(pUHD15-1)
1
207
MSR
tetR
SGSDPSIHTR
VP16
YGGF
tTA$_S$
406
490
(pUHD151-1)
b
Xho I
Sst I Kpn Sma Sal
TCCCTATCAGTGATAGAGA
7
(pUHC 13-3)
-53
-31
+1
+75
CTCGAG
AGGCCTATATAA
luc
(A)n
Xho I
(T)
Sac II
TCTCTATCACTGATAGGGA
7
(pUHC13-4)
Sal Sma Kpn Sst I
Xho I

Fig. 1

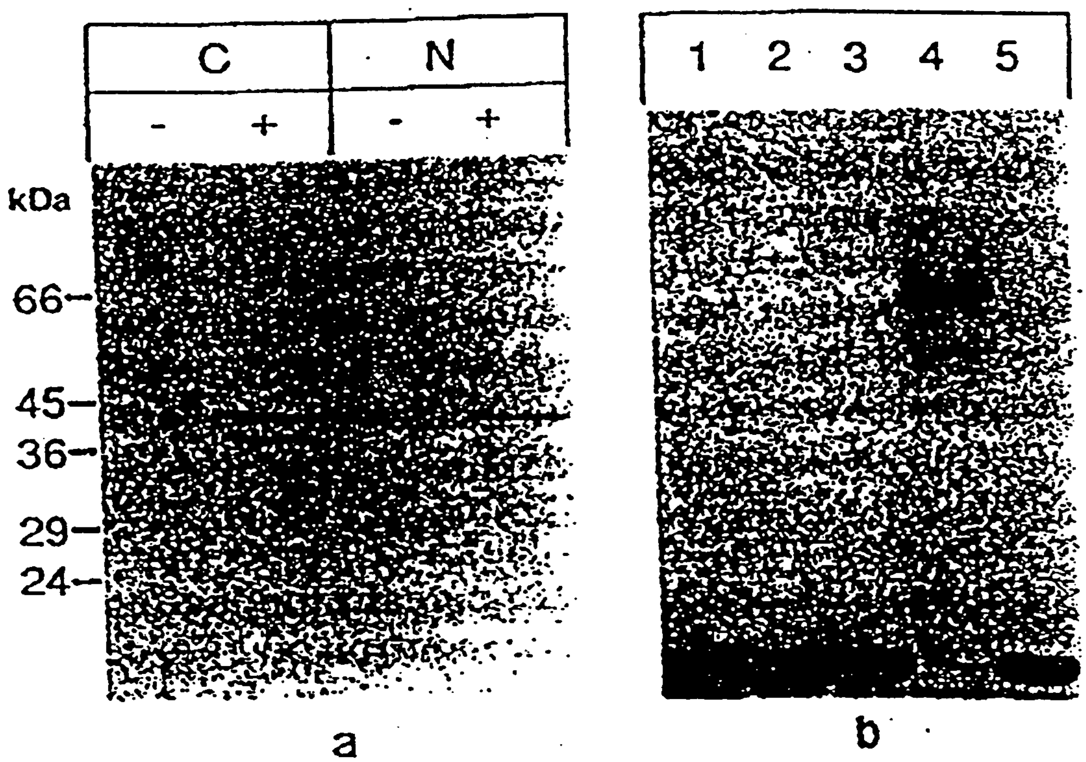


Fig. 2

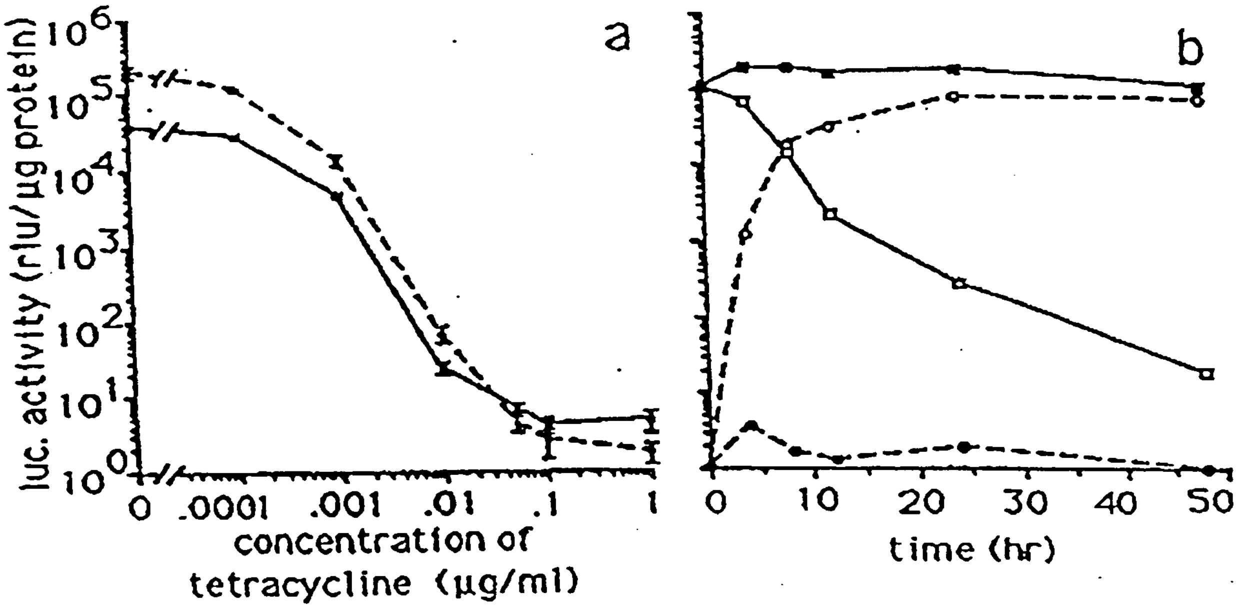

a
b
luc. activity (rlu/µg protein)
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0 .0001 .001 .01 .1 1
concentration of
tetracycline (µg/ml)
0 10 20 30 40 50
time (hr)

Fig. 3

```
1/1                                     31/11
ATG TCT AGA TTA GAT AAA AGT AAA GTG ATT AAC AGC GCA TTA GAG CTG CTT AAT GAG GTC
Met ser arg leu asp lys ser lys val ile asn ser ala leu glu leu leu asn glu val
61/21                                   91/31
GGA ATC GAA GGT TTA ACA ACC CGT AAA CTC GCC CAG AAG CTA GGT GTA GAG GAG CCT ACA
gly ile glu gly leu thr thr arg lys leu ala gln lys leu gly val glu glu pro thr
121/41                                  151/51
TTG TAT TGG CAT GTA AAA AAT AAG CGG GCT TTG CTC GAC GCC TTA GCC ATT GAG ATG TTA
leu tyr trp his val lys asn lys arg ala leu leu asp ala leu ala ile glu met leu
181/61                                  211/71
GAT AGG CAC CAT ACT CAC TTT TGC CCT TTA GAA GGG GAA AGC TGG CAA GAT TTT TTA CGT
asp arg his his thr his phe cys pro leu glu gly glu ser trp gln asp phe leu arg
241/81                                  271/91
AAT AAG GCT AAA AGT TTT AGA TGT GCT TTA CTA AGT CAT CGC GAT GGA GCA AAA GTA CAT
asn lys ala lys ser phe arg cys ala leu leu ser his arg asp gly ala lys val his
301/101                                 331/111
TTA GGT ACA CGG CCT ACA GAA AAA CAG TAT GAA ACT CTC GAA AAT CAA TTA GCC TTT TTA
leu gly thr arg pro thr glu lys gln tyr glu thr leu glu asn gln leu ala phe leu
361/121                                 391/131
TGC CAA CAA GGT TTT TCA CTA GAG AAT GCA TTA TAT GCA CTC AGC GCT GTG GGG CAT TTT
cys gln gln gly phe ser leu glu asn ala leu tyr ala leu ser ala val gly his phe
421/141                                 451/151
ACT TTA GGT TGC GTA TTG GAA GAT CAA GAG CAT CAA GTC GCT AAA GAA GAA AGG GAA ACA
thr leu gly cys val leu glu asp gln glu his gln val ala lys glu glu arg glu thr
481/161                                 511/171
CCT ACT ACT GAT AGT ATG CCG CCA TTA TTA CGA CAA GCT ATC GAA TTA TTT GAT CAC CAA
pro thr thr asp ser met pro pro leu leu arg gln ala ile glu leu phe asp his gln
541/181                                 571/191
GGT GCA GAG CCA GCC TTC TTA TTC GGC CTT GAA TTG ATC ATA TGC GGA TTA GAA AAA CAA
gly ala glu pro ala phe leu phe gly leu glu leu ile ile cys gly leu glu lys gln
601/201                                 631/211
CTT AAA TGT GAA AGT GGG TCC GCG TAC AGC CGC GCG CGT ACG AAA AAC AAT TAC GGG TCT
leu lys cys glu ser gly ser ala tyr ser arg ala arg thr lys asn asn tyr gly ser
661/221                                 691/231
ACC ATC GAG GGC CTG CTC GAT CTC CCG GAC GAC GAC GCC CCC GAA GAG GCG GGG CTG GCG
thr ile glu gly leu leu asp leu pro asp asp asp ala pro glu glu ala gly leu ala
721/241                                 751/251
GCT CCG CGC CTG TCC TTT CTC CCC GCG GGA CAC ACG CGC AGA CTG TCG ACG GCC CCC CCG
ala pro arg leu ser phe leu pro ala gly his thr arg arg leu ser thr ala pro pro
781/261                                 811/271
ACC GAT GTC AGC CTG GGG GAC GAG CTC CAC TTA GAC GGC GAG GAC GTG GCG ATG GCG CAT
thr asp val ser leu gly asp glu leu his leu asp gly glu asp val ala met ala his
841/281                                 871/291
GCC GAC GCC CTA GAC GAT TTC GAT CTG GAC ATG TTG GGG GAC GGG GAT TCC CCG GGT CCG
ala asp ala leu asp asp phe asp leu asp met leu gly asp gly asp ser pro gly pro
901/301                                 931/311
GGA TTT ACC CCC CAC GAC TCC GCC CCC TAC GGC GCT CTG GAT ATG GCC GAC TTC GAG TTT
gly phe thr pro his asp ser ala pro tyr gly ala leu asp met ala asp phe glu phe
961/321                                 991/331
GAG CAG ATG TTT ACC GAT CCC CTT GGA ATT GAC GAG TAC GGT GGG TAG
glu gln met phe thr asp pro leu gly ile asp glu tyr gly gly AMB
```

Fig. 4

```
1/1                                         31/11
ATG TCT AGA TTA GAT AAA AGT AAA GTG ATT AAC AGC GCA TTA GAG CTG CTT AAT GAG GTC
Met ser arg leu asp lys ser lys val ile asn ser ala leu glu leu leu asn glu val
61/21                                       91/31
GGA ATC GAA GGT TTA ACA ACC CGT AAA CTC GCC CAG AAG CTA GGT GTA GAG CAG CCT ACA
gly ile glu gly leu thr thr arg lys leu ala gln lys leu gly val glu gln pro thr
121/41                                      151/51
TTG TAT TGG CAT GTA AAA AAT AAG CGG GCT TTG CTC GAC GCC TTA GCC ATT GAG ATG TTA
leu tyr trp his val lys asn lys arg ala leu leu asp ala leu ala ile glu met leu
181/61                                      211/71
GAT AGG CAC CAT ACT CAC TTT TGC CCT TTA GAA GGG GAA AGC TGG CAA GAT TTT TTA CGT
asp arg his his thr his phe cys pro leu glu gly glu ser trp gln asp phe leu arg
241/81                                      271/91
AAT AAC GCT AAA AGT TTT AGA TGT GCT TTA CTA AGT CAT CGC GAT GGA GCA AAA GTA CAT
asn asn ala lys ser phe arg cys ala leu leu ser his arg asp gly ala lys val his
301/101                                     331/111
TTA GGT ACA CGG CCT ACA GAA AAA CAG TAT GAA ACT CTC GAA AAT CAA TTA GCC TTT TTA
leu gly thr arg pro thr glu lys gln tyr glu thr leu glu asn gln leu ala phe leu
361/121                                     391/131
TGC CAA CAA GGT TTT TCA CTA GAG AAT GCA TTA TAT GCA CTC AGC GCT GTG GGG CAT TTT
cys gln gln gly phe ser leu glu asn ala leu tyr ala leu ser ala val gly his phe
421/141                                     451/151
ACT TTA GGT TGC GTA TTG GAA GAT CAA GAG CAT CAA GTC GCT AAA GAA GAA AGG GAA ACA
thr leu gly cys val leu glu asp gln glu his gln val ala lys glu glu arg glu thr
481/161                                     511/171
CCT ACT ACT GAT AGT ATG CCG CCA TTA TTA CGA CAA GCT ATC GAA TTA TTT GAT CAC CAA
pro thr thr asp ser met pro pro leu leu arg gln ala ile glu leu phe asp his gln
541/181                                     571/191
GGT GCA GAG CCA GCC TTC TTA TTC GGC CTT GAA TTG ATC ATA TGC GGA TTA GAA AAA CAA
gly ala glu pro ala phe leu phe gly leu glu leu ile ile cys gly leu glu lys gln
601/201                                     631/211
CTT AAA TGT GAA AGT GGG TCT GAT CCA TCG ATA CAC ACG CGC AGA CTG TCG ACG GCC CCC
leu lys cys glu ser gly ser asp pro ser ile his thr arg arg leu ser thr ala pro
661/221                                     691/231
CCG ACC GAT GTC AGC CTG GGG GAC GAG CTC CAC TTA GAC GGC GAG GAC GTG GCG ATG GCG
pro thr asp val ser leu gly asp glu leu his leu asp gly glu asp val ala met ala
721/241                                     751/251
CAT GCC GAC GCG CTA GAC GAT TTC GAT CTG GAC ATG TTG GGG GAC GGG GAT TCC CCG GGT
his ala asp ala leu asp asp phe asp leu asp met leu gly asp gly asp ser pro gly
781/261                                     811/271
CCG GGA TTT ACC CCC CAC GAC TCC GCC CCC TAC GGC GCT CTG GAT ATG GCC GAC TTC GAG
pro gly phe thr pro his asp ser ala pro tyr gly ala leu asp met ala asp phe glu
841/281                                     871/291
TTT GAG CAG ATG TTT ACC GAT GCC CTT GGA ATT GAC GAG TAC GGT GGG TTC TAG
phe glu gln met phe thr asp ala leu gly ile asp glu tyr gly gly phe AMB
```

Fig. 5

GAATTCCTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTC
CCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGT
GAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCC
TATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGA
AAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGCTCGGTACCCGGGT
CGAGTAGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGC
CTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGC
GG

Fig. 6

GAATTCCTCGACCCGGGTACCGAGCTC*GACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTA*

AACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCT

ATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAA

CTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTAT

CACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACT

CGAGTAGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGC

CTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGC

GG

Fig. 7

GAGCTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTC
TATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAA
ACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTA
TCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAAC
TCGACTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAACTCGAGATCCGGCGAATTCGAAC
ACGCAGATGCAGTCGGGGCGGCGCGGTCCGAGGTCCACTTCGCATATTAAGGTGACGCGTGTGG
CCTCGAACACCGAG

Fig. 8

Fig. 9A

CTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATC
AGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGT
CGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAG
TGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCG
AGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGCTCGGTACCCGGGTCGAGTA
GGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAG
ACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCCC
GAATTCGAGCTCGGTACCCGGGCCCCCCCTCGAGGTCGACGGTATCGATAAGCTTGATATCGAAT
TCCAGGAGGTGGAGATCCGCGGGTCCAGCCAAACCCCACACCCATTTTCTCCTCCCTCTGCCCC
TATATCCCGGCACCCCCTCCTCCTAGCCCTTTCCCTCCTCCCGAGAGACGGGGGAGGAGAAAAG
GGGAGTTCAGGTCGACATGACTGAGCTGAAGGCAAAGGAACCTCGGGCTCCCCACGTGGCGGGC
GGCGCGCCCTCCCCCACCGAGGTCGGATCCCAGCTCCTGGGTCGCCCGGACCCTGGCCCCTTCC
AGGGGAGCCAGACCTCAGAGGCCTCGTCTGTAGTCTCCGCCATCCCCATCTCCCTGGACGGGTT
GCTCTTCCCCCGGCCCTGTCAGGGGCAGAACCCCCCAGACGGGAAGACGCAGGACCCACCGTCG
TTGTCAGACGTGGAGGGCGCATTTCCTGGAGTCGAAGCCCCGGAGGGGGCAGGAGACAGCAGCT
CGAGACCTCCAGAAAAGGACAGCGGCCTGCTGGACAGTGTCCTCGACACGCTCCTGGCGCCCTC
GGGTCCCGGGCAGAGCCACGCCAGCCCTGCCACCTGCGAGGCCATCAGCCCGTGGTGCCTGTTT
GGCCCCGACCTTCCCGAAGACCCCCGGCTGCCCCCGCTACCAAAGGGGTGTTGGCCCCGCTCA
TGAGCCGACCCGAGGACAAGGCAGGCGACAGCTCTGGACGGCAGCGGCCCACAAGGTGCTGCC
CAGGGGACTGTCACCATCCAGGCAGCTGCTGCTCCCCTCCTCTGGGAGCCCTCACTGGCCGGCA
GTGAAGCCATCCCCGCAGCCCGCTGCGGTGCAGGTAGACGAGGAGGACAGCTCCGAATCCGAGG
GCACCGTGGGCCCGCTCCTGAAGGGCCAACCTCGGGCACTGGGAGGCACGGCGGCCGGAGGAGG
AGCTGCCCCCGTCGCGTCTGGAGCGGCCGCAGGAGGCGTCGCCCTTGTCCCCAAGGAAGATTCT
CGCTTCTCGGCGCCCAGGGTCTCCTTGGCGGAGCAGGACGCGCCGGTGGCGCCTGGGCGCTCCC
CGCTGGCCACCTCGGTGGTGGATTTCATCCACGTGCCCATCCTGCCTCTCAACCACGCTTTCCT
GGCCACCCGCACCAGGCAGCTGCTGGAGGGGGAGAGCTACGACGGCGGGGCCGCGGCCGCCAGC
CCCTTCGTCCCGCAGCGGGGCTCCCCCTCTGCCTCGTCCACCCCTGTGGCGGGCGGCGACTTCC
CCGACTGCACCTACCCGCCCGACGCCGAGCCCAAAGATGACGCGTTCCCCCTCTACGGCGACTT
CCAGCCGCCCGCCCTCAAGATAAAGGAGGAGGAAGAAGCCGCCGAGGCCGCGGCGCGCTCCCCG
CGTACGTACCTGGTGGCTGGTGCAAACCCCGCCCGCCTTCCCGGACTTCCAGCTGGCAGCGCCGC
CGCCACCCTCGCTGCCGCCTCGAGTGCCCTCGTCCAGACCCGGGGAAGCGGCGGTGGCGGCCTC

Fig. 9B

CCCAGGCAGTGCCTCCGTCTCCTCCTCGTCCTCGTCGGGGTCGACCCTGGAGTGCATCCGTGTAC
AAGGCAGAAGGCGCGCCGCCCCAGCAGGGCCCCTTCGCGCCGCTGCCCTGCAAGCCTCCGGGCG
CCGGCGCCTGCCTGCTCCCGCGGGACGGCCTGCCCTCCACCTCCGCCTCGGGCGCAGCCGCCGG
GGCCGCCCCTGCGCTCTACCCGACGCTCGGCCTCAACGGACTCCCGCAACTCGGCTACCAGGCC
GCCGTGCTCAAGGAGGGCCTGCCGCAGGTCTACACGCCCTATCTCAACTACCTGAGGCCGGATT
CAGAAGCCAGTCAGAGCCCACAGTACAGCTTCGAGTCACTACCTCAGAAGATTTGTTTGATCTG
TGGGGATGAAGCATCAGGCTGTCATTATGGTGTCCTCACCTGTGGGAGCTGTAAGGTCTTCTTT
AAAAGGGCAATGGAAGGGCAGCATAACTATTTATGTGCTGGAAGAAATGACTGCATTGTTGATA
AAATCCGCAGGAAAAACTGCCCGGCGTGTCGCCTTAGAAAGTGCTGTCAAGCTGGCATGGTCCT
TGGAGGGCGAAAGTTTAAAAAGTTCAATAAAGTCAGAGTCATGAGAGCACTCGATGCTGTTGCT
CTCCCACAGCCAGTGGGCATTCCAAATGAAAGCCAACGAATCACTTTTTCTCCAAGTCAAGAGA
TACAGTTAATTCCCCCTCTAATCAACCTGTTAATGAGCATTGAACCAGATGTGATCTATGCAGG
ACATGACAACACAAAGCCTGATACCTCCAGTTCTTTGCTGACGAGTCTTAATCAACTAGGCGAG
CGGCAACTTCTTTCAGTGGTAAAATGGTCCAAATCTCTTCCAGGTTTTCGAAACTTACATATTG
ATGACCAGATAACTCTCATCCAGTATTCTTGGATGAGTTTAATGGTATTTGGACTAGGATGGAG
ATCCTACAAACATGTCAGTGGGCAGATGCTGTATTTTGCACCTGATCTAATATTAAATGAACAG
CGGATGAAAGAATCATCATTCTATTCACTATGCCTTACCATGTGGCAGATACCGCAGGAGTTTG
TCAAGCTTCAAGTTAGCCAAGAAGAGTTCCTCTGCATGAAAGTATTACTACTTCTTAATACAAT
TCCTTTGGAAGGACTAAGAAGTCAAAGCCAGTTTGAAGAGATGAGATCAAGCTACATTAGAGAG
CTCATCAAGGCAATTGGTTTGAGGCAAAAAGGAGTTGTTTCCAGCTCACAGCGTTTCTATCAGC
TCACAAAACTTCTTGATAACTTGCATGATCTTGTCAAACAACTTCACCTGTACTGCCTGAATAC
ATTTATCCAGTCCCGGGCGCTGAGTGTTGAATTTCCAGAAATGATGTCTGAAGTTATTGCTGCA
CAGTTACCCAAGATATTGGCAGGGATGGTGAAACCACTTCTCTTTCATAAAAAGTGAATGTCAA
TTATTTTTCAAAGAATTAAGTGTTGTGGTATGTCTTTCGTTTTGGTCAGGATTATGACGTCTCG
AGTTTTTATAATATTCTGAAAGGGAATTCCTGCAGCCCGGGGGATCCACTAGTTCTAGAGGATC
CAGACATGATAAGATACATTGATGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATG
CTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAA
GTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTT
AAAGCAAGTAAAACCTCTACAAATGTGGTATGGCTGATTATGATCCTGCAAGCCTCGTCGTCTG
GCCGGACCACGCTATCTGTGCAAGGTCCCCGGACGCGCGCTCCATGAGCAGAGCGCCCGCCGCC
GAGGCAAGACTCGGGCGGCGCCCTGCCCGTCCCACCAGGTCAACAGGCGGTAACCGGCCTCTTC
ATCGGGAATGCGGCGACCTTCAGCATCGCCGGCATGTCCCCTGGCGGACGGAAGTATCAGCT
CGACCAAGCTTGGCGAGATTTTCAGGAGCTAAGGAAGCTAAAATGGAGAAAAAAATCACTGGAT
ATACCACCGTTGATATATCCCAATGGCATCGTAAAGAACATTTTGAGGCATTTCAGTCAGTTGC
TCAATGTACCTATAACCAGACCGTTCAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGC
GGTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGC
TGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAA
CGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTG
CTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGA
GGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCG

Fig. 9C

CTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG
GCGCTTTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG
GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGA
GTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGA
GCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAA
GGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTC
TTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACG
CGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGA
ACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCT
TTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGT
TACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTG
CCTGACTCCCCGTCGTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGC
AATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGA
AGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC
GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGG
CATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGG
CGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTG
TCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTAC
TGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAA
TAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATA
GCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTT
ACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTT
ACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAA
GGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCA
GGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTT
CCGCGCACATTTCCCCGAAAAGTGCCACCTGACGTCTAAGAAACCATTATTATCATGACATTAA
CCTATAAAAATAGGCGTATCACGAGGCCCTTTCGTC

Fig. 10A

CTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATC
AGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGT
CGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAG
TGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCG
AGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGCTCGGTACCCGGGTCGAGTA
GGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAG
ACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCCC
GAATTCCGGCCACGACCATGACCATGACCCTCCACACCAAAGCATCTGGGATGGCCCTACTGCA
TCAGATCCAAGGGAACGAGCTGGAGCCCCTGAACCGTCCGCAGCTCAAGATCCCCCTGGAGCGG
CCCCTGGGCGAGGTGTACCTGGACAGCAGCAAGCCCGCCGTGTACAACTACCCCGAGGGCGCCG
CCTACGAGTTCAACGCCGCGGCCGCCGCCAACGCGCAGGTCTACGGTCAGACCGGCCTCCCCTA
CGGCCCCGGGTCTGAGGCTGCGGCGTTCGGCTCCAACGGCCTGGGGGGTTTCCCCCCACTCAAC
AGCGTGTCTCCGAGCCCGCTGATGCTACTGCACCCGCCGCCGCAGCTGTCGCCTTTCCTGCAGC
CCCACGGCCAGCAGGTGCCCTACTACCTGGAGAACGAGCCCAGCGGCTACACGGTGCGCGAGGC
CGGCCCGCCGGCATTCTACAGGCCAAATTCAGATAATCGACGCCAGGGTGGCAGAGAAAGATTG
GCCAGTACCAATGACAAGGGAAGTATGGCTATGGAATCTGCCAAGGAGACTCGCTACTGTGCAG
TGTGCAATGACTATGCTTCAGGCTACCATTATGGAGTCTGGTCCTGTGAGGGCTGCAAGGCCTT
CTTCAAGAGAAGTATTCAAGGACATAACGACTATATGTGTCCAGCCACCAACCAGTGCACCATT
GATAAAAACAGGAGGAAGAGCTGCCAGGCCTGCCGGCTCCGCAAATGCTACGAAGTGGGAATGA
TGAAAGGTGGGATACGAAAAGACCGAAGAGGAGGGAGAATGTTGAAACACAAGCGCCAGAGAGA
TGATGGGGAGGGCAGGGGTGAAGTGGGGTCTGCTGGAGACATGAGAGCTGCCAACCTTTGGCCA
AGCCCGCTCATGATCAAACGCTCTAAGAAGAACAGCCTGGCCTTGTCCCTGACGGCCGACCAGA
TGGTCATGGCCTTGTTGGATGCTGAGCCCCCCATACTCTATTCCGAGTATGATCCTACCAGACC
CTTCAGTGAAGCTTCGATGATGGGCTTACTGACCAACCTGGCAGACAGGGAGCTGGTTCACATG
ATCAACTGGGCGAAGAGGGTGCCAGGCTTTGTGGATTTGACCCTCCATGATCAGGTCCACCTTC
TAGAATGTGCCTGGCTAGAGATCCTGATGATTGGTCTCGTCTGGCGCTCCATGGAGCACCCAGT
GAAGCTACTGTTTGCTCCTAACTTGCTCTTGGACAGGAACCAGGGAAAATGTGTAGAGGGCATG
GTGGAGATCTTCGACATGCTGCTGGCTACATCATCTCGGTTCCGCATGATGAATCTGCAGGGAG
AGGAGTTTGTGTGCCTCAAATCTATTATTTTGCTTAATTCTGGAGTGTACACATTTCTGTCCAG
CACCCTGAAGTCTCTGGAAGAGAAGGACCATATCCACCGAGTCCTGGACAAGATCACAGACACT
TTGATCCACCTGATGGCCAAGGCAGGCCTGACCCTGCAGCAGCAGCACCAGCGGCTGGCCCAGC
TCCTCCTCATCCTCTCCCACATCAGGCACATGAGTAACAAAGGCATGGAGCATCTGTACAGCAT
GAAGTGCAAGAACGTGGTGCCCCTCTATGACCTGCTGCTGGAGATGCTGGACGCCCACCGCCTA
CATGCGCCCACTAGCCGTGGAGGGGCATCCGTGGAGGAGACGGACCAAAGCCACTTGGCCACTG
CGGGCTCTACTTCATCGCATTCCTTGCAAAAGTATTACATCACGGGGGAGGCAGAGGGTTTCCC
TGCCACAGTCTGAGAGCTCCCTGGCGGAATTCGAGCTCGGTACCCGGGGATCCTCTAGAGGATC
CAGACATGATAAGATACATTGATGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATG
CTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAA
GTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTT
AAAGCAAGTAAAACCTCTACAAATGTGGTATGGCTGATTATGATCCTGCAAGCCTCGTCGTCTG

Fig. 10B

GCCGGACCACGCTATCTGTGCAAGGTCCCCGGACGCGCGCTCCATGAGCAGAGCGCCCGCCGCC
GAGGCAAGACTCGGGCGGCGCCCTGCCCGTCCCACCAGGTCAACAGGCGGTAACCGGCCTCTTC
ATCGGGAATGCGCGCGACCTTCAGCATCGCCGGCATGTCCCCTGGCGGACGGGAAGTATCAGCT
CGACCAAGCTTGGCGAGATTTTCAGGAGCTAAGGAAGCTAAAATGGAGAAAAAAATCACTGGAT
ATACCACCGTTGATATATCCCAATGGCATCGTAAAGAACATTTTGAGGCATTTCAGTCAGTTGC
TCAATGTACCTATAACCAGACCGTTCAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGC
GCTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGC

TGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAA
CGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTG
CTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGA
GGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCG
CTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG
GCGCTTTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG
GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGA
GTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGA
GCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAA
GGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTC
TTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACG
CGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGA
ACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCT
TTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGT
TACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTG
CCTGATCCCCGTCGTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCA
ATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAA
GGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCG
GGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGC
ATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGC
GAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGT
CAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACT
GTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAAT
AGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATAG
CAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTA
CCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTA
CTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAG
GGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAG
GGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTC
CGCGCACATTTCCCCGAAAAGTGCCACCTGACGTCTAAGAAACCATTATTATCATGACATTAAC
CTATAAAAATAGGCGTATCACGAGGCCCTTTCGTC

Fig. 11

Conditional Knock-Out Strategy 1

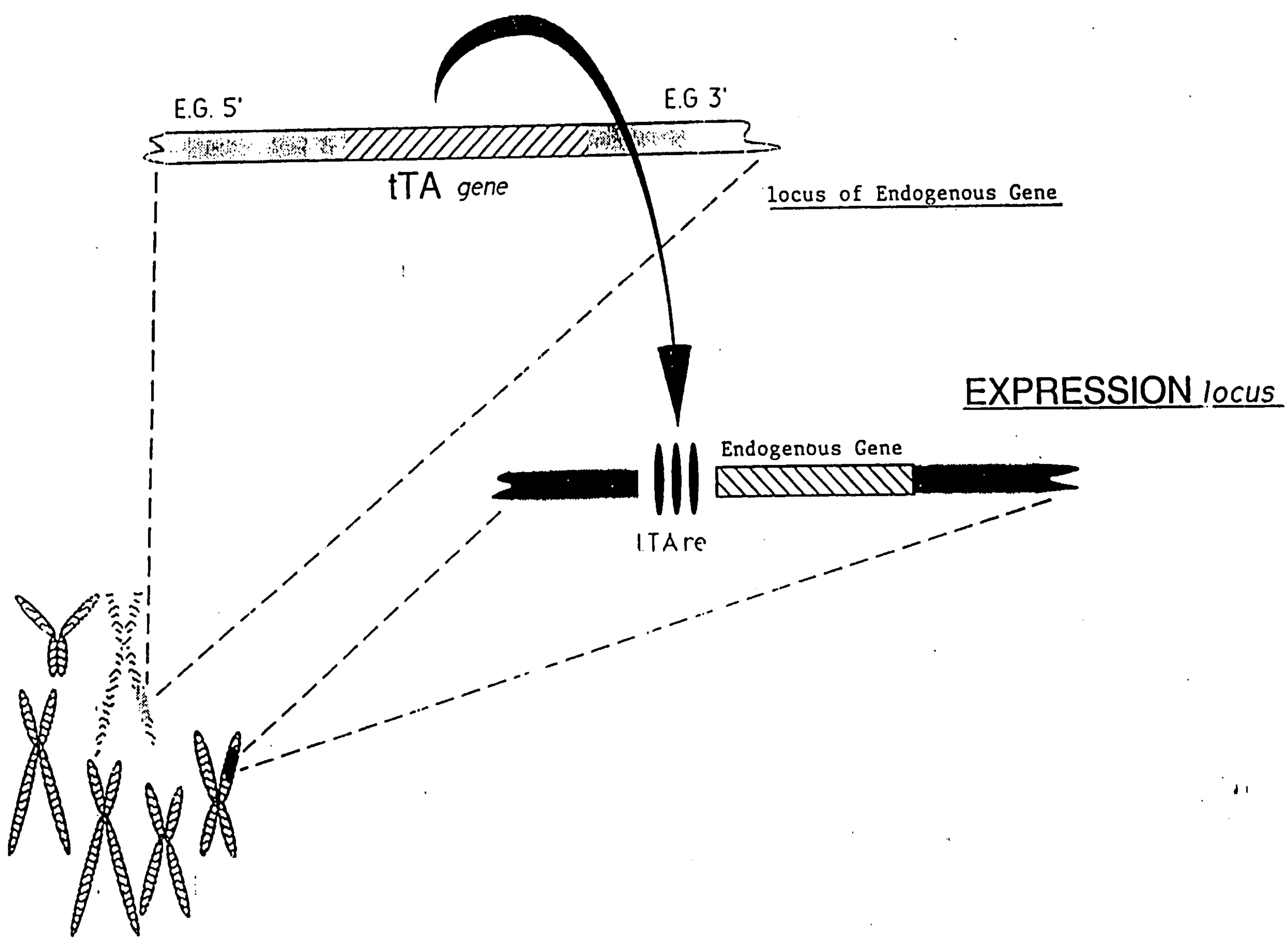
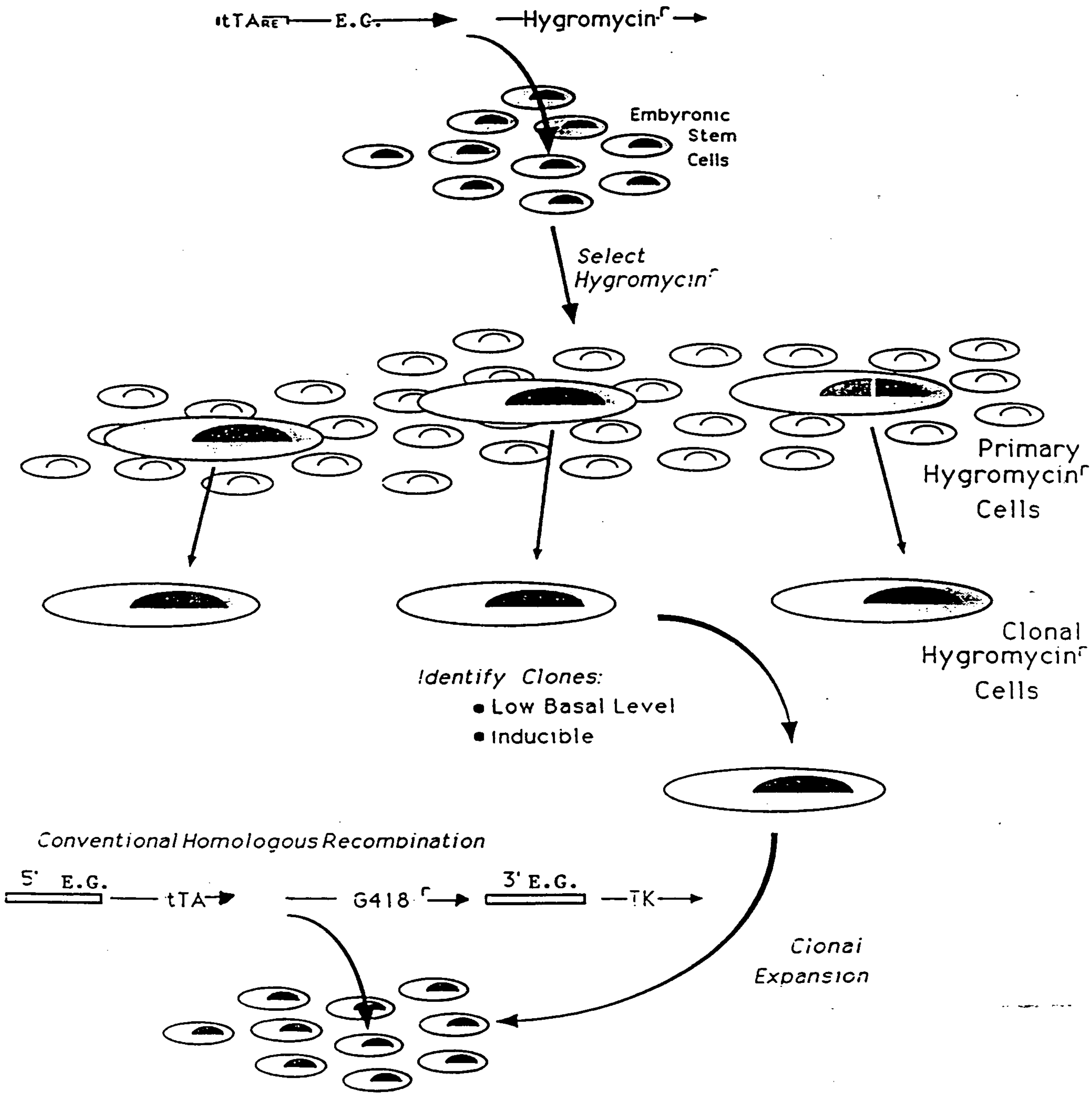


Fig. 12

Conditional Knock-Out Strategy 2

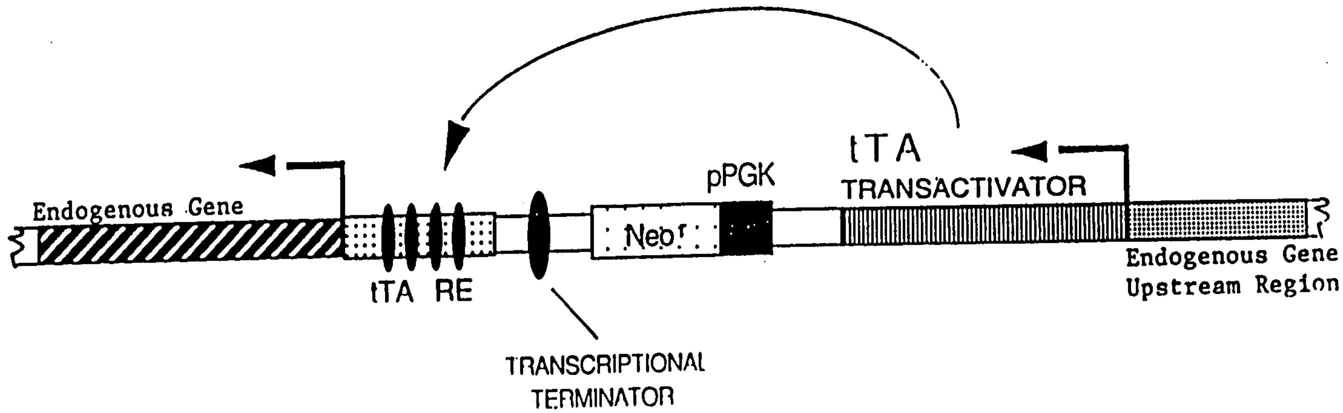


Identify clones with low basal activity of endogenous gene (near untransformed levels).
Identify among these those which respond to tTA (by transient expression).
Perform homologous recombination into endogenous locus.

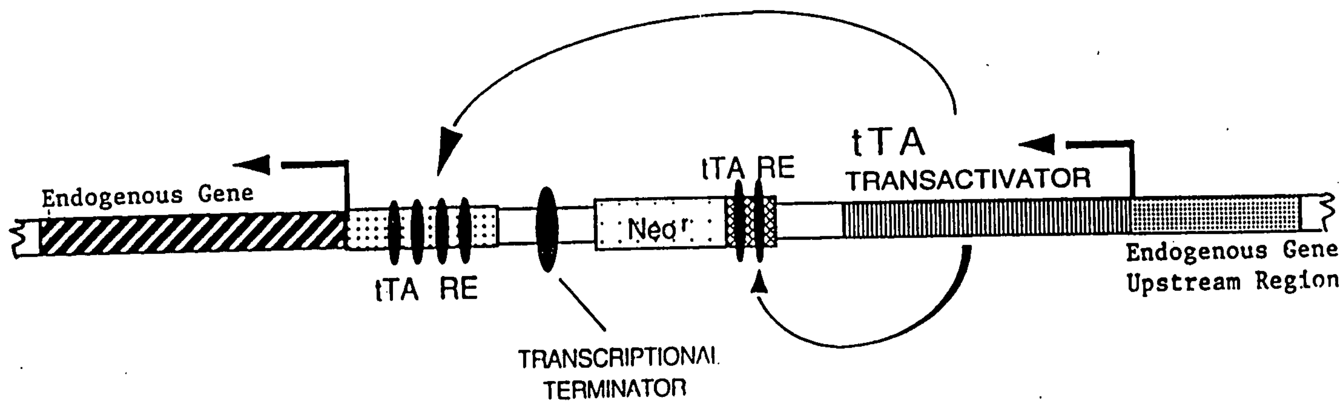
Fig. 13

Conditional Knock-Out Strategy 3

A.



B.



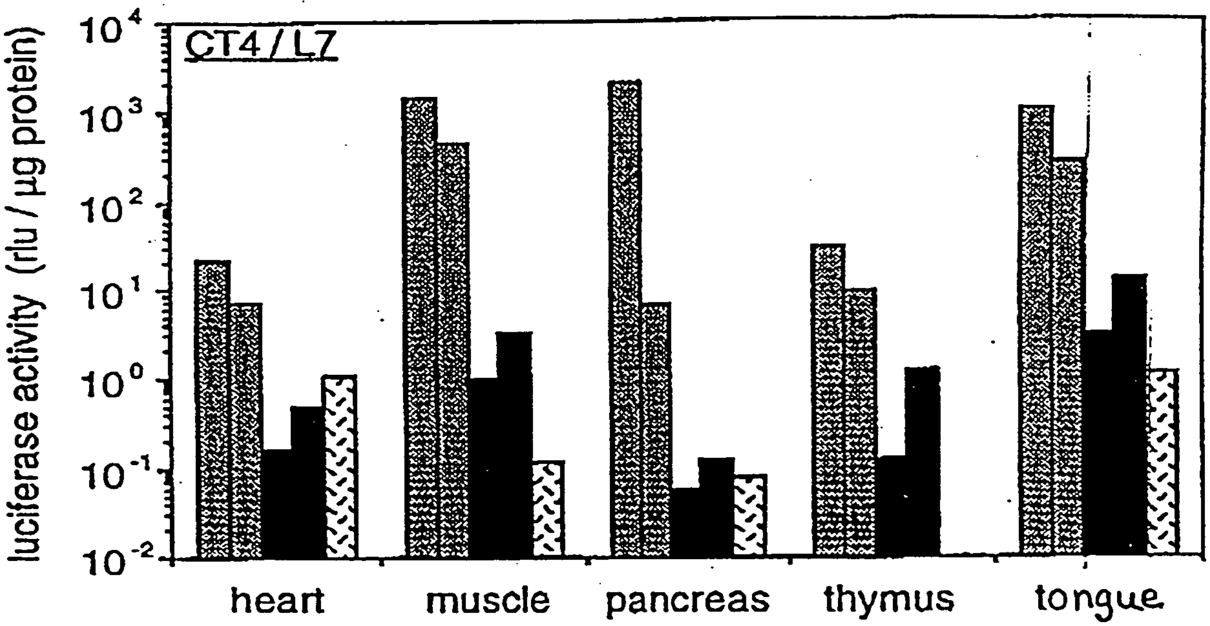

CT4 / L7
luciferase activity (rlu / µg protein)
10⁴
10³
10²
10¹
10⁰
10⁻¹
10⁻²
heart
muscle
pancreas
thymus
tongue

Figure 14